VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 27 and 28 have been deleted without prejudice and disclaimer.

REMARKS

Introductory Comments:

Claims 1-47 were pending in the application. Applicants note with appreciation that the Office has acknowledged applicants' election of Group I, claims 1-25 and 27-47, as provided for in the Response filed 26 September 2001. As a result, claims 6, 8-11, 13-14 and 26 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Accordingly, claims 1-5, 7, 12, 15-25 and 27-47 are currently under consideration and were examined in the Office Action dated 6 December 2001. In the Action, the Office has asserted the following claim rejections: (1) claims 27 and 28 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite; (2) claims 27 and 28 stand rejected under 35 U.S.C.§101 as containing improper subject matter; (3) claims 1, 16 and 27-47 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled; (4) claims 1, 2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, 46 and 47 stand rejected under 35 U.S.C. § 102(e) as unpatentable over US Patent No. 5,925,362 to Spitler et al. ("Spitler"); and (5) claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44 and 45 stand rejected under 35 U.S.C. §103(a) as unpatentable over Spitler in view of Fynan et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:11478-11482 ("Fynan"), Golding et al. (1994) *Am. J. Trop. Med. Hyg.* 50(4):33-40 ("Golding"), and Sedegah et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:9866-9870 ("Sedegah"). Applicants respectfully traverse these rejections for the following reasons.

Overview of the Amendment:

Applicants, by way of this response, have cancelled claims 27 and 28 without prejudice and disclaimer. It is to be understood that cancellation of these claims is not meant to be an acquiescence to any rejection raised in the application, and applicants expressly reserve the right to bring the claims again in a subsequent, related application.

The Rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §101:

Claims 27 and 28 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office has objected that the claims do not set forth proper method/process limitations. The claims stand rejected under 35 U.S.C. §101 for the same reasons.

In response, applicants draw the Office's attention to the amendment tendered with the instant response, whereby claims 27 and 28 have been cancelled. Accordingly, the rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §101 have been rendered moot.

The Rejection under 35 U.S.C. §112, first paragraph:

Claims 1, 16 and 27-47 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. In particular, the Office has focused upon one embodiment of the claimed invention, wherein the claimed compositions include an "immune shift lipid adjuvant." Office Action at page 4. The Office then objects that applicants have not provided sufficient disclosure on the basis that: (a) only a single antigen is exemplified (CEA); (b) the single exemplified antigen is not from an

infectious or parasitic disease causing organism; (c) the exemplification was carried out in mice; (d) there "are several factors which significantly affect the generation of Th1 versus a Th2 response to an antigen; and (e) the combination of all of these issues means that "it would have required undue experimentation to practice the invention as claimed." Applicants respectfully traverse.

Applicants' burden under Section 112 is merely to provide a specification that enables a person reasonably skilled in the art to make and use the claimed invention without undue experimentation. The fact that some experimentation may be employed, however, does not make it undue if a person of skill in the art typically engages in such experimentation. This is because the prohibition is against "undue experimentation," not merely "experimentation." *In re Angstadt*, 190 USPQ 214 (CCPA 1976).

With regard to the Office's assertion that the claims are limited exclusively to traditional "immune shift" adjuvants, applicants wish to draw the Office's attention to the Examples (pages 33-49) where numerous different antigen/adjuvant combinations have been assembled according to the claimed invention and then demonstrated to have the recited features in working, art-recognized animal model systems. In this regard, claim 1 recites a composition having a nucleic acid encoding an antigen combined with an adjuvant "effective to enhance at least one component of an immune response against the encoded antigen." Although these recited composition may include an adjuvant that acts as a traditional "immune shift" adjuvant (an adjuvant that does provide a measurable shift in an immune response from one T helper subset to another), other non-DNA adjuvants can also be used in the compositions, that is, those that are effective to enhance at least one component

of an immune response. That is why applicants chose to recite their invention in the form of pending claim 1.

Applicants have amply demonstrated their recited inventions using MPL adjuvant combined with DNA encoding an CEA antigen (Example 1), Quil A adjuvant combined with DNA encoding an influenza virus NP antigen (Examples 2 and 3); Quil A adjuvant combined with DNA encoding an HIV virus gp120 antigen (Example 4); and Quil A adjuvant combined with DNA encoding a hepatitis B virus surface antigen (Example 5). In each of these working examples, applicants demonstrated that the addition of the non-DNA adjuvant to the nucleic acid composition enhanced at least one component of the immune response against the encoded antigen as required by the claims.

With respect to the Office's objections that applicants have only exemplified their invention with human carcino embryonic antigen (CEA) which is not from an infectious or parasitic agent, applicants initially draw the Office's attention to the Examples where antigens from influenza virus, HIV virus and hepatitis B virus were also tested. In addition, applicants note that the human CEA protein is an antigen in the mouse model since it is clearly not a native protein. Accordingly, the Office's objection that applicants only exemplified a single, non-infectious antigen system is incorrect. Applicants exemplified their claims throughout their scope using 4 entirely different antigen (CEA, HIV, influenza and HBV).

With respect to the Office's objection that applicants merely carried out studies in the art-recognized mouse model system, applicants are frankly at a loss to understand the statutory basis for this ground of objection. Applicants have provided a detailed disclosure of the non-DNA adjuvants and antigen-encoding

sequences that are to be used in the practice of the invention, where to find the sequence information for such antigens, how to go about obtaining the sequences, how to select appropriate control sequences, how operably link antigen sequences to control sequences to obtain an expression cassette, how to insert the expression cassettes into numerous different vector systems, and how to administer these various vector systems to obtain expression of the antigens of interest. See applicants' specification at pages 17-33. Although not required under Section 112 (*In re Robbins*, 166 U.S.P.Q. 552 (CCPA 1970)), applicants have exemplified their thoroughly enabling disclosure with a number of working examples using art-recognized animal model systems.

What the Office seems to suggest is that the mouse model is simply not suitable for exemplifying immunological compositions, and that absent actual human clinical data, applicants' specification cannot be enabling for human applications. This apparent requirement that applicants must have actually carried out human studies is improper and not supported by any statutory rule. This is because were such a requirement actually valid, it would discourage inventors from disclosing and teaching their discoveries for the public's benefit until an exhaustive experimental study into any and all possible embodiments had been completed, which discouragement is antithetical and in direct contradiction of the guiding principals underlying Section 112. See, e.g., *Rohm & Hass Co. v. Dawson Chemical Co.*, 217 USPQ 515, 563-564 (S.D. Tex. 1983), *rev'd on other grounds*, 220 USPQ 289 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Applicants have provided sufficient enabling disclosure for their recited compositions and methods for using those compositions, and have even provided numerous working examples

in art-accepted animal model. Although the Office has argued that human cytokine patterns may be more complex than murine patterns, there is no valid technical basis for the premise that the mouse animal model would **not** be predictive for humans, and there is frankly no valid reason to doubt that applicant's compositions will be entirely suitable for use in other animals such as humans. The Office has thus failed in its burden to provide a reasonable basis to question the enablement that applicant has provided *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). In fact, the only way to supplant applicants' presumptively correct disclosure (supported by multiple working examples) is to completely ignore or discount the experimental showing that applicants have provided. This is improper since applicants' disclosure must be viewed as in compliance with the enablement requirement of Section 112, unless there is reason to doubt the objective truth thereof. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

Finally, with regard to the Office's objection that there are "several factors which significantly affect the generation of Th1 versus a Th2 response to an antigen" and that "it would have required undue experimentation to practice the invention as claimed," applicants note that the determination of whether or not something is indeed undue experimentation must be judged by the standards of those skilled in the art. Applicants submit that, given the level of skill in the art which is generally acknowledged to be high in the fields of immunology and molecular biology, the detailed description provided by the specification, and the numerous working examples, a skilled artisan could readily practice the claimed invention without undue experimentation. See, e.g., *Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed.

Cir. 1988), and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Applicants have provided more than sufficient disclosure regarding how to make and use their recited compositions, and have exemplified this disclosure with express working examples. The skilled artisan would thus have no difficulty in following applicants' directions to test other compositions for their ability to enahce an aspect of an immune response in a suitable subject. Although some experimentation may need to be carried out, the mere fact that some experimentation may be required to practice the invention throughout its entire scope does not necessarily make it "undue," particularly when the level of skill in the art is typically high, and such experimentation is routinely carried out. It is well settled that satisfaction of the enablement requirement of Section 112 is not precluded by the necessity for some experimentation such as routine screening.

Accordingly, the rejection of claims 1, 16 and 27-47 under 35 U.S.C. §112, first paragraph, is improper and simply not supported by any evidence of record in the case. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Rejection under 35 U.S.C. §102(e):

Claims 1-2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, 46 and 47 stand rejected under 35 U.S.C. §102(e) as anticipated by Spitler. In particular, the Office asserts that Spitler discloses the combination of a non-DNA adjuvant and an antigen-encoding nucleic acid sequence. Applicants strongly disagree.

The Office has directed applicants' attention to columns 7-8, 9-10 and claims 1-8 of Spitler in support of its assertion. However, on a careful review of these sections of Spitler, it is clear the Spitler fails to teach or even so much as suggest that a non-DNA adjuvant be combined with a nucleic acid encoding an antigen in a single composition. Columns 7-9 of Spitler describe various PSA antigen formulations where the disclosure shifts back and forth between describing conventional vaccine compositions (e.g., compositions containing PSA protein or peptide) and nucleic acid compositions that contain a sequence encoding a PSA antigen. However, applicants submit that the Office has read this section in an incorrect way so as to combine non-DNA adjuvants with DNAs encoding PSA antigens. At column 7, line 47, Spitler et al. start to describe liposomal compositions where "the prostate antigens may also include immune system adjvuants." Note that Spitler et al. are discussing the antigens (i.e., PSA peptides or proteins) in this sentence, not nucleic acid sequences that would encode these antigens. The rest of the paragraph discusses suitable adjuvant, and then ends with the statement "... may also be incorporated with antigen into the liposome." Spitler, column 7, line 56. Here again, Spitler et al. are discussing the peptide/protein antigens, not sequences encoding these antigens. The next paragraph (column 7, line 57) begins with the statement "The prostate antigen may also be formulated with various adjuvants ...". Here again, Spitler et al, are clearly referring to the protein/peptide PSA antigens, not nucleic acid sequences that would encode these antigens. The next paragraph, however, starts to discuss DNAs encoding PSA antigens (Spitler, column 8, line 3). Here, Spitler et al. start "In an additional formulation, the DNA encoding proteins .... is administered in a viral expression

vector." Note that Spitler are clearly referring to DNAs that encode an antigen, and that these compositions are treated entirely separately and distinctly from the earlier compositions that were protein/peptide antigen compositions. The paragraph ends by merely discussing the various forms of nucleic acid administration that can be used including viral vectors, "naked" DNA administration, or administration of a DNA (per se) in a liposomal formulation. There is absolutely no disclosure whatsoever that can be found in Spitler that relates to the combination of a non-DNA adjuvant with a nucleic acid encoding an antigen.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)). Finally, in order to anticipate, a prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986).

Spitler clearly fails to anticipate applicants' recited invention since it does not provide any disclosure whatsoever regarding applicants' recited combination of nucleic acid and non-DNA components. Since Spitler never even contemplated

such a combination, the reference cannot be considered to be enabling, thus placing the allegedly disclosed matter in the possession of the public. Applicants submit that the Office's rejection is based upon an incorrect reading of Spitler, where portions of the specification dealing with peptide/protein antigen compositions has been incorrectly combined with other sections of the specification that deal with DNA compositions that encode an antigen. Since Spitler does not disclose applicants' particular combination, it does not disclose each and every element of the claims as required under Section 102, and thus fails to anticipate applicants' invention.

For all of the foregoing reasons, then, the rejection of claims1-2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, 46 and 47 under 35 U.S.C. §102(e) is improper. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Rejection under 35 U.S.C. §103(a):

Claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42 and 42-45 stand were rejected under 35 U.S.C. §103(a) as unpatentable over Spitler in view of Fynan, Golding and Sedegah. In particular, the Office relies upon Spitler as the primary reference for the same reasons as discussed in the Section 102 rejection, and then combines this with the secondary references to find gene gun delivery techniques (Fynan), use of a malaria antigen (Sedegah) and use MPL as an immune shift adjuvant (Golding). The Office then concludes that "it would have been *prima facie* obvious to the skilled artisan to immunize an animal with a composition comprising a plasmid encoding an antigen and an immune shift adjuvant such as MPL." Applicants respectfully traverse.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its proposed combination.

More particularly, as demonstrated above, the primary reference (Spitler) fails to teach or even so much as suggest that a non-DNA adjuvant should be combined with, e.g., a DNA encoding antigen in a single composition. The Office's assertion that Spitler does teach such a composition is based upon a clear misreading of the Spitler disclosure. The secondary references to Fynan, Golding and Sedegah likewise fail to teach such a novel combination, and the Office has not asserted otherwise. Accordingly, the rejection fails to teach or suggest all of applicants' recited claim limitations. Since the cited prior art fails to teach or suggest applicants' recited combination compositions, there cannot have been a reasonable expectation for success for such compositions. Accordingly, the Office has failed to establish a *prima facie* showing of obviousness over its proposed

combination since the proposed combination and each component thereof fails to teach or suggest all of applicants' recited claim limitations. Accordingly, the rejection of claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42 and 42-45 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 6 June 2002

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